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(54) Title: ANALOGS OF PARATHYROID HORMONE			
(57) Abstract			
<p>Peptide variants of fragment (1-34) of parathyroid hormone, in which at least one of the amino acid residues at positions 7, 11, 23, 24, 27, 28 and 31 is cyclohexylalanine, or at least one of the amino acid residues at positions 3, 16, 17, 18, 19 and 34 is α-aminoisobutyric acid; or, alternatively, at least the amino acid residue at position 1 is α,β-diaminopropionic acid, the amino acid residue at position 27 is homoarginine, or the amino acid residue at position 31 is norleucine.</p>			

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ANALOGS OF PARATHYROID HORMONE

Background of the Invention

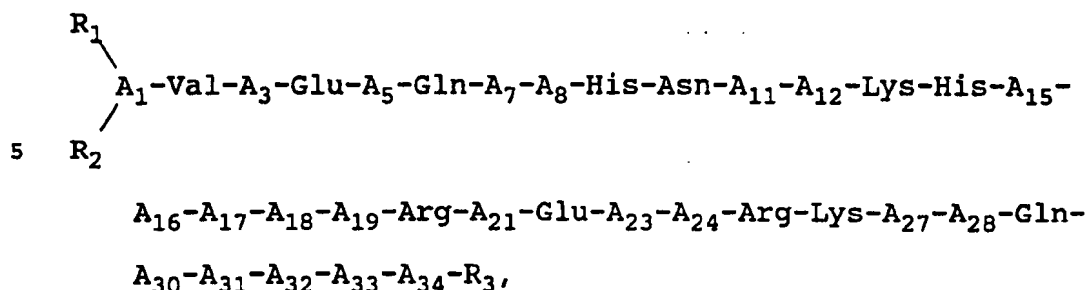
Parathyroid hormone ("PTH") is a polypeptide
5 produced by the parathyroid glands. The mature
circulating form of the hormone is comprised of 84 amino
acid residues. The biological action of PTH can be
reproduced by a peptide fragment of its N-terminus (e.g.
amino acid residues 1 through 34). Parathyroid hormone-
10 related protein ("PTHrP") is a 139 to 173 amino
acid-protein with N-terminal homology to PTH. PTHrP
shares many of the biological effects of PTH including
binding to a common PTH/PTHrP receptor. Tregear, et al.,
Endocrinol., 93:1349 (1983). PTH peptides from many
15 different sources, e.g., human, bovine, rat, chicken,
have been characterized. Nissenson, et al., Receptor,
3:193 (1993).

PTH has been shown to both improve bone mass and
quality. Dempster, et al., Endocrine Rev., 14:690
20 (1993); and Riggs, Amer. J. Med., 91 (Suppl. 5B):37S
(1991). The anabolic effect of intermittently
administered PTH has been observed in osteoporotic men
and women either with or without concurrent
antiresorptive therapy. Slovik, et al., J. Bone Miner.
25 Res., 1:377 (1986); Reeve, et al., Br. Med. J., 301:314
(1990); and Hesch, R-D., et al., Calcif. Tissue Int'l,
44:176 (1989).

Summary of the Invention

In one aspect, the invention relates to peptide
30 variants of PTH(1-34) of the following generic formula:

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wherein

- A_1 is Ser, Ala, or Dap;
- 10 A_3 is Ser, Thr, or Aib;
- A_5 is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe or p-X-Phe, in which X is OH, a halogen, or CH_3 ;
- A_7 is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3 ;
- 15 A_8 is Met, Nva, Leu, Val, Ile, Cha, or Nle;
- A_{11} is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe or p-X-Phe in which X is OH, a halogen, or CH_3 ;
- A_{12} is Gly or Aib;
- A_{15} is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe, 20 or p-X-Phe in which X is OH, a halogen, or CH_3 ;
- A_{16} is Ser, Asn, Ala, or Aib;
- A_{17} is Ser, Thr, or Aib;
- A_{18} is Met, Nva, Leu, Val, Ile, Nle, Cha, or Aib;
- A_{19} is Glu or Aib;
- 25 A_{21} is Val, Cha, or Met;
- A_{23} is Trp or Cha;
- A_{24} is Leu or Cha;
- A_{27} is Lys, Aib, Leu, hArg, Gln, or Cha;
- A_{28} is Leu or Cha;
- 30 A_{30} is Asp or Lys;
- A_{31} is Val, Nle, Cha, or deleted;
- A_{32} is His or deleted;
- A_{33} is Asn or deleted;
- A_{34} is Phe, Tyr, Amp, Aib, or deleted;

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each of R_1 and R_2 is, independently, H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} naphthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynaphthylalkyl; or

5 one and only one of R_1 and R_2 is COE_1 in which E_1 is C_{1-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} naphthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxy-phenylalkyl, or C_{11-20} hydroxynaphthylalkyl; and

R_3 is OH, NH_2 , C_{1-12} alkoxy, or $NH-Y-CH_2-Z$ in which

10 Y is a C_{1-12} hydrocarbon moiety and Z is H, OH, CO_2H , or $CONH_2$;

provided that (i) at least one of A_5 , A_7 , A_8 , A_{11} , A_{15} , A_{18} , A_{21} , A_{23} , A_{24} , A_{27} , A_{28} , and A_{31} is Cha, or at least one of A_3 , A_{12} , A_{16} , A_{17} , A_{18} , A_{19} , and A_{34} is Aib;

15 or that (ii) at least A_1 is Dap, A_7 is β -Nal, Trp, Pal, Phe, or p-X-Phe, A_{15} is β -Nal, Trp, Pal, Phe, or p-X-Phe, A_{27} is hArg, or A_{31} is Nle; or a pharmaceutically acceptable salt thereof.

A subset of the compounds covered by the above

20 formula are those in which at least one of A_5 , A_7 , A_{11} , A_{15} , A_{18} , A_{21} , A_{23} , A_{24} , A_{27} , A_{28} , and A_{31} is Cha. For example, A_3 is Ser; A_5 is Ile; A_7 is Leu or Cha; A_8 is Met, Nva, Leu, Val, Ile, or Nle; A_{11} is Leu or Cha; A_{12} is Gly; A_{15} is Leu or Cha; A_{16} is Asn or Aib; A_{17} is Ser; A_{18}

25 is Met or Nle; A_{21} is Val; A_{27} is Lys, hArg, or Cha; A_{32} is His; A_{31} is Val, Nle, or Cha; A_{33} is Asn; A_{34} is Phe, Tyr, Amp, or Aib; R_1 is H; R_2 is H; and R_3 is NH_2 ;

provided that at least one of A_5 , A_7 , A_8 , A_{11} , A_{15} , A_{18} , A_{21} , A_{23} , A_{24} , A_{27} , A_{28} , and A_{31} is Cha, or at least one of

30 A_3 , A_{12} , A_{16} , A_{17} , A_{18} , A_{19} , and A_{34} is Aib. If desired, at least one of A_7 and A_{11} can be Cha; or at least one of A_{15} , A_{23} , A_{24} , A_{27} , A_{28} , and A_{31} is Cha.

In another subset, at least one of A_3 , A_{12} , A_{16} , A_{17} , A_{18} , A_{19} , and A_{34} is Aib. For example, A_3 is Ser or

35 Aib; A_5 is Ile; A_7 is Leu or Cha; A_8 is Met, Nva, Leu,

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Val, Ile, or Nle; A₁₁ is Leu or Cha; A₁₅ is Leu or Cha, A₁₆ is Asn or Aib; A₁₈ is Met, Aib, or Nle; A₂₁ is Val; A₂₇ is Lys, Aib, Leu, hArg, or Cha; A₃₁ is Val, Nle, or Cha; A₃₂ is His; A₃₃ is Asn; A₃₄ is Phe, Tyr, Amp, or Aib; R₁ is H; R₂ is H; and R₃ is NH₂; provided that at least one of A₅, A₇, A₈, A₁₁, A₁₅, A₁₈, A₂₁, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha, or at least one of A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, and A₃₄ is Aib. If desired, at least one of A₇ and A₁₁ can be Cha; or at least one of A₁₅, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha.

In a still further subset, at least one of A₅, A₇, A₈, A₁₁, A₁₅, A₁₈, A₂₁, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha, or at least one of A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, and A₃₄ is Aib. For example, A₃ is Ser or Aib; A₅ is Ile; A₇ is Leu or Cha; A₈ is Met, Nva, Leu, Val, Ile, or Nle; A₁₁ is Leu or Cha; A₁₅ is Leu or Cha; A₁₆ is Asn or Aib; A₁₈ is Met, Aib, or Nle; A₂₁ is Val; A₂₇ is Lys, Aib, Leu, hArg, or Cha; A₃₁ is Val, Nle, or Cha; A₃₂ is His; A₃₃ is Asn; A₃₄ is Phe, Tyr, Amp, or Aib; R₁ is H; R₂ is H; and R₃ is NH₂. If desired, at least one of A₇ and A₁₁ is Cha and at least one of A₁₆, A₁₉, and A₃₄ is Aib; or at least one of A₂₄, A₂₈, and A₃₁ is Cha and at least one of A₁₆ and A₁₇ is Aib.

In yet another subset, at least one of A₁ is Dap, A₇ is β -Nal, Trp, Pal, Phe or p-X-Phe, A₁₃ is β -Nal, Trp, Pal, Phe, or p-X-Phe. For example, A₁ is Ser, Gly, or Dap; A₃ is Ser or Aib; A₈ is Met, Nva, Leu, Val, Ile, or Nle; A₁₆ is Asn or Aib; A₁₈ is Met, Aib, or Nle; A₂₁ is Val; A₂₇ is Lys, Aib, Leu, hArg, or Cha; A₃₁ is Val, Nle, or Cha; A₃₂ is His; A₃₃ is Asn; A₃₄ is Phe, Tyr, Amp, or Aib; R₁ is H; R₂ is H; and R₃ is NH₂.

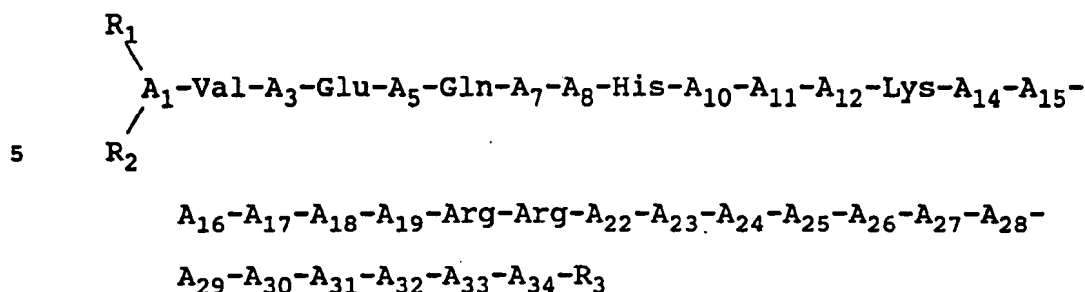
The following are examples of the peptide of this invention as covered by the above formula: [Cha⁷]hPTH(1-34)NH₂; [Cha¹¹]hPTH(1-34)NH₂; [Cha¹⁵]hPTH(1-34)NH₂; [Cha^{7, 11}]hPTH(1-34)NH₂; [Cha^{7, 11}, Nle^{8, 18}, Tyr³⁴]hPTH(1-34)NH₂; [Cha²³]hPTH(1-34)NH₂; [Cha²⁴]hPTH(1-34)NH₂; [Nle^{8, 18},

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Cha²⁷]hPTH(1-34)NH₂; [Cha²⁸]hPTH(1-34)NH₂; [Cha³¹]hPTH(1-
 34)NH₂; [Cha²⁷]hPTH(1-34)NH₂; [Cha^{27, 29}]hPTH(1-34)NH₂;
 [Cha²⁸]bPTH(1-34)NH₂; [Cha²⁸]rPTH(1-34)NH₂; [Cha^{24, 28,}
 31]hPTH(1-34)NH₂; [Aib¹⁶]hPTH(1-34)NH₂; [Aib¹⁹]hPTH(1-
 5 34)NH₂; [Aib³⁴]hPTH(1-34)NH₂; [Aib^{16, 19}]hPTH(1-34)NH₂;
 [Aib^{16, 19, 34}]bPTH(1-34)NH₂; [Aib^{16, 34}]hPTH(1-34)NH₂;
 [Aib^{19, 34}]hPTH(1-34)NH₂; [Cha<sup>7, 11, Nle^{8, 18, Aib^{16, 19,}}
 Tyr³⁴]hPTH(1-34)NH₂; [Cha<sup>7, 11, Nle^{8, 18, 31, Aib^{16, 19,}}
 Tyr³⁴]hPTH(1-34)NH₂; [Cha^{7, Aib¹⁶}]hPTH(1-34)NH₂; [Cha^{11,}
 10 Aib¹⁶]hPTH(1-34)₂; [Cha^{7, Aib³⁴}]hPTH(1-34)NH₂; [Cha^{11,}
 Aib³⁴]hPTH(1-34)NH₂; [Cha^{27, Aib¹⁶}]hPTH(1-34)NH₂; [Cha^{27,}
 Aib³⁴]hPTH(1-34)NH₂; [Cha^{28, Aib¹⁶}]hPTH(1-34)NH₂; [Cha^{28,}
 Aib³⁴]hPTH(1-34)NH₂; [Nle³¹]hPTH(1-34)NH₂; [hArg²⁷]hPTH(1-
 34)NH₂; [Dap<sup>1, Nle^{8, 18, Tyr³⁴}]hPTH(1-34)NH₂;
 15 [Nle³¹]bPTH(1-34)NH₂; [Nle³¹]rPTH(1-34)NH₂; [hArg²⁷]bPTH(1-
 34)NH₂; [hArg²⁷]rPTH(1-34)NH₂; [Cha^{7, 11, Aib^{19,}}
 Lys³⁰]hPTH(1-34)NH₂; [Aib¹²]hPTH(1-34)NH₂; [Cha^{24, 28, 31,}
 Lys³⁰]hPTH(1-34)NH₂; [Cha^{28, 31}]hPTH(1-34)NH₂; [Cha^{7, 11,}
 Nle^{8, 18, Aib³⁴}]hPTH(1-34)NH₂; [Aib³]hPTH(1-34)NH₂;
 20 [Cha⁸]hPTH(1-34)NH₂; [Cha¹⁵]hPTH(1-34)NH₂; [Cha^{7, 11,}
 Aib¹⁹]hPTH(1-34)NH₂; [Cha^{7, 11, Aib¹⁶}]hPTH(1-34)NH₂;
 [Aib¹⁷]hPTH(1-34)NH₂; [Cha⁵]hPTH(1-34)NH₂; [Cha^{7, 11,}
 15]hPTH(1-34)NH₂; [Cha<sup>7, 11, Nle^{8, 18, Aib^{19,}}
 Tyr³⁴]hPTH(1-34)NH₂; [Cha<sup>7, 11, Nle^{8, 18, Aib^{19, Lys^{30,}}}
 25 Tyr³⁴]hPTH(1-34)NH₂; [Cha^{7, 11, 15}]hPTH(1-34)NH₂;
 [Aib¹⁷]hPTH(1-34)NH₂; [Cha^{7, 11, Leu²⁷}]hPTH(1-34)NH₂;
 [Cha^{7, 11, 15, Leu²⁷}]hPTH(1-34)NH₂; [Cha^{7, 11, 27}]hPTH(1-
 34)NH₂; [Cha^{7, 11, 15, 27}]hPTH(1-34)NH₂; [Trp¹⁵]hPTH(1-
 34)NH₂; [Nal¹⁵]hPTH(1-34)NH₂; [Trp^{15, Cha²³}]hPTH(1-34)NH₂;
 30 [Cha^{15, 23}]hPTH(1-34)NH₂; [Phe^{7, 11}]hPTH(1-34)NH₂; [Nal^{7,}
 11]hPTH(1-34)NH₂; [Trp^{7, 11}]hPTH(1-34)NH₂; [Phe^{7, 11,}
 15]hPTH(1-34)NH₂; [Nal^{7, 11, 15}]hPTH(1-34)NH₂; [Trp^{7, 11,}
 15]hPTH(1-34)NH₂; and [Tyr^{7, 11, 15}]hPTH(1-34)NH₂..</sup></sup></sup></sup></sup>

In another aspect, this invention relates to
 35 peptides covered by the following formula:

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wherein

- $$\begin{array}{l}
 A_1 \text{ is Ala, Ser, or Dap;} \\
 A_3 \text{ is Ser or Aib;} \\
 A_5 \text{ is His, Ile, or Cha;} \\
 A_7 \text{ is Leu, Cha, Nle, } \beta\text{-Nal, Trp, Pal,} \\
 \text{Phe, or p-X-Phe in which X is OH, a halogen, or CH}_3\text{;} \\
 A_8 \text{ is Leu, Met, or Cha;} \\
 A_{10} \text{ is Asp or Asn;} \\
 A_{11} \text{ is Lys, Leu, Cha, Phe, or } \beta\text{-Nal;} \\
 A_{12} \text{ is Gly or Aib;} \\
 A_{14} \text{ is Ser or His;} \\
 A_{15} \text{ is Ile, or Cha;} \\
 A_{16} \text{ is Gln or Aib;} \\
 A_{17} \text{ is Asp or Aib;} \\
 A_{18} \text{ is Leu, Aib, or Cha;} \\
 A_{19} \text{ is Arg or Aib;} \\
 A_{22} \text{ is Phe, Glu, Aib, or Cha;} \\
 A_{23} \text{ is Phe, Leu, Lys, or Cha;} \\
 A_{24} \text{ is Leu, Lys, or Cha;} \\
 A_{25} \text{ is His, Aib, or Glu;} \\
 A_{26} \text{ is His, Aib, or Lys;} \\
 A_{27} \text{ is Leu, Lys, or Cha;} \\
 A_{28} \text{ is Ile, Leu, Lys, or Cha;} \\
 A_{29} \text{ is Ala, Glu, or Aib;} \\
 A_{30} \text{ is Glu, Cha, Aib, or Lys;} \\
 A_{31} \text{ is Ile, Leu, Cha, Lys, or deleted;} \\
 A_{32} \text{ is His or deleted;} \\
 A_{33} \text{ is Thr or deleted;}
 \end{array}$$

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A₃₄ is Ala or deleted;

each of R₁ and R₂ is, independently, H,

C₁₋₁₂ alkanyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀ naphthylalkyl, C₁₋₁₂, hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀

5 hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; or one and only one of R₁ and R₂ is COE₁ in which E₁ is C₁₋₁₂ alkyl, C₂₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀ naphthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀ hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; and

10 R₃ is OH, NH₂, C₁₋₁₂ alkoxy, or NH-Y-CH₂-Z in which Y is a C₁₋₁₂ hydrocarbon moiety and Z is H, OH, CO₂H or CONH₂;

provided that (i) at least one of A₅, A₇, A₈, A₁₁, A₁₅, A₁₈, A₂₂, A₂₃, A₂₄, A₂₇, A₂₈, A₃₀, or A₃₁ is Cha, or at
 15 least one of A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, A₂₂, A₂₅, A₂₆, A₂₉, A₃₀, or A₃₄ is Aib; or that (ii) at least one of A₂₃, A₂₄, A₂₇, A₂₈, or A₃₁ is Lys; or a pharmaceutically acceptable salt thereof. In one embodiment, at least one of A₇ and A₁₁ is Cha. In another embodiment, at least one
 20 of A₁₆ or A₁₉ is Aib. Specific examples of peptides of the just-recited formula include, but are not limited to,
 [Cha⁷]hPTHrP(1-34)NH₂; [Cha¹¹]hPTHrP(1-34)NH₂; [Cha⁷,
 11]hPTHrP(1-34)NH₂; [Aib¹⁶, Tyr³⁴]hPTHrP(1-34)NH₂;
 [Aib¹⁹]hPTHrP(1-34)NH₂; [Aib¹⁶, 19]hPTHrP(1-34)NH₂; [Cha⁷,
 25 11, Aib¹⁶]hPTHrP(1-34)NH₂; [Cha⁷, 11, Aib¹⁹]hPTHrP(1-34)NH₂;
 [Cha²², Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 30}]hPTHrP(1-34)NH₂;
 [Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 27, 30}]hPTHrP(1-34)NH₂;
 [Cha^{22, 23}, Glu^{25, 29}, Leu^{28, 31}, Lys^{26, 30}]hPTHrP(1-34)NH₂;
 [Glu^{22, 25}, Leu^{23, 28, 31}, Aib²⁹, Lys^{26, 30}]hPTHrP(1-34)NH₂;
 30 [Glu^{22, 25, 29}, Lys^{23, 26, 30}, Leu^{28, 31}]hPTHrP(1-34)NH₂;
 [Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys²⁶, Cha³⁰]hPTHrP(1-34)NH₂;
 [Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys²⁶, Aib³⁰]hPTHrP(1-34)NH₂;
 [Glu^{22, 25, 29}, Leu^{23, 31}, Lys^{26, 28, 30}]hPTHrP(1-34)NH₂;
 [Cha^{22, 23, 24, 27, 28, 31}, Glu^{25, 29}, Lys^{26, 30}]hPTHrP(1-
 35 34)NH₂; [Glu^{22, 25, 29}, Cha^{23, 24, 28, 31}, Lys^{26, 27},

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- ³⁰]hPTHrP(1-34)NH₂; [Glu^{22, 25, 29}, Cha^{23, 24, 27, 31}, Lys^{26, 28, 30}]hPTHrP(1-34)NH₂; [Glu^{22, 25, 29}, Lys^{23, 26, 30}, Cha^{24, 27, 28, 31}]hPTHrP(1-34)NH₂; [Cha²², Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 27, 30}] hPTHrP(1-34)NH₂; [Cha²², Leu^{23, 31}, Glu^{25, 29}, Lys^{26, 28, 30}]hPTHrP(1-34)NH₂; [Cha²², Lys^{23, 26, 30}, Glu^{25, 29}, Leu^{28, 31}]hPTHrP(1-34)NH₂; [Cha²², Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 30}, Aib²⁹] hPTHrP(1-34)NH₂; [Cha²², Leu^{23, 28, 31}, Glu^{25, 29}, Lys²⁶, Aib³⁰]hPTHrP(1-34)NH₂; [Glu^{22, 25}, Leu^{23, 28, 31}, Lys^{26, 27, 30}, Aib²⁹]hPTHrP(1-34)NH₂; [Glu^{22, 25}, Lys^{23, 26, 30}, Leu^{28, 31}, Aib²⁹] hPTHrP(1-34)NH₂; [Glu^{22, 25}, Leu^{23, 31}, Lys^{26, 28, 30}, Aib²⁹]hPTHrP(1-34)NH₂; [Cha^{7, 11}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 30}] hPTHrP(1-34)NH₂; [Cha^{7, 11, 22}, Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Cha^{7, 11}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 27, 30}] hPTHrP(1-34)NH₂; [Cha^{7, 11, 22, 23}, Glu^{25, 29}, Leu^{28, 31}, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Cha^{7, 11}, Glu^{22, 25, 29}, Lys^{23, 26, 30}, Leu^{28, 31}]hPTHrP(1-34)NH₂; [Cha^{7, 11}, Glu^{22, 25, 29}, Leu^{23, 31}, Lys^{26, 28, 30}] hPTHrP(1-34)NH₂; [Cha^{7, 11}, Glu^{22, 25}, Leu^{23, 28, 31}, Aib²⁹, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Cha^{7, 11}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys²⁶, Aib³⁰]hPTHrP(1-34)NH₂; [Cha¹⁵, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 30}]hPTHrP(1-34) NH₂; [Cha^{15, 22}, Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Cha¹⁵, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 27, 30}]hPTHrP(1-34)NH₂; [Cha^{15, 22, 23}, Glu^{25, 29}, Leu^{28, 31}, Lys^{26, 30}]hPTHrP(1-34) NH₂; [Cha¹⁵, Glu^{22, 25}, Leu^{23, 28, 31}, Aib²⁹, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Cha¹⁵, Glu^{22, 25, 29}, Lys^{23, 26, 30}, Leu^{28, 31}]hPTHrP(1-34) NH₂; [Cha¹⁵, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys²⁶, Aib³⁰] hPTHrP(1-34)NH₂; [Cha¹⁵, Glu^{22, 28, 29}, Leu^{23, 31}, Lys^{26, 28, 30}]hPTHrP(1-34)NH₂; [Cha^{15, 30}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys²⁶]hPTHrP(1-34)NH₂; [Cha^{7, 8, 22}, Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Cha^{7, 8}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 27, 30}]hPTHrP(1-34)NH₂; [Cha^{7, 8, 22, 23}, Glu^{25, 29}, Leu^{28, 31}, Lys^{26, 30}] hPTHrP (1-34)NH₂; [Cha^{7, 8}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 30}] hPTHrP(1-34)NH₂; [Cha^{7, 8},

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Glu^{22, 25}, Leu^{23, 28, 31}, Aib²⁹, Lys^{26, 30}]hPTHrP(1-34) NH₂;
 [Cha^{7, 8}, Glu^{22, 25, 29}, Lys^{23, 26, 30}, Leu^{28, 31}]hPTHrP(1-
 34)NH₂; [Cha^{7, 8}, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys²⁶, Aib³⁰]
 hPTHrP(1-34)NH₂; [Cha^{7, 8}, Glu^{22, 25, 29}, Leu^{23, 31}, Lys²⁶,
 5 28, 30]hPTHrP(1-34)NH₂; [Cha^{7, 8, 30}, Glu^{22, 25, 29}, Leu^{23, 28,}
 31, Lys²⁶]hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Cha^{7, 11, 22}, Met⁸,
 Asn¹⁰, His¹⁴, Leu^{23, 28, 31}, Glu^{25, 29}, Lys^{26, 30}]hPTHrP(1-34)
 NH₂; [Ser¹, Ile⁵, Cha^{7, 11}, Met⁸, Asn¹⁰, His¹⁴, Glu^{22, 25,}
 29, Leu^{23, 28, 31}, Lys^{26, 27, 30}]hPTHrP(1-34)NH₂; [Ser¹,
 10 Ile⁵, Cha^{7, 11}, Met⁸, Asn¹⁰, His¹⁴, Glu^{22, 25, 29}, Leu^{23, 31},
 Lys^{26, 28, 30}]hPTHrP(1-34)NH₂; Ser¹, Ile⁵, Cha^{7, 11}, Met⁸,
 Asn¹⁰, His¹⁴, Glu^{22, 25, 29}, Lys^{23, 26, 30}, Leu^{28,}
 31]hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Cha^{7, 11}, Met⁸, Asn¹⁰,
 His¹⁴, Glu^{22, 25}, Leu^{23, 28, 31}, Aib²⁹, Lys^{26, 30}]hPTHrP(1-34)
 15 NH₂; [Ser¹, Ile⁵, Cha^{7, 11}, Met⁸, Asn¹⁰, His¹⁴, Glu^{22, 25,}
 29, Leu^{23, 28, 31}, Lys²⁶, Aib³⁰] PTHrP(1-34)NH₂; [Ser¹,
 Ile⁵, Cha^{7, 11, 22, 23}, Met⁸, Asn¹⁰, His¹⁴, Glu^{25, 29}, Leu^{28,}
 31, Lys^{26, 30}]hPTHrP(1-34) NH₂; [Ser¹, Ile⁵, Cha^{7, 11, 15},
 Met⁸, Asn¹⁰, His¹⁴]hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Met⁸,
 20 Asn¹⁰, Leu¹¹, His¹⁴, Aib¹⁶]hPTHrP (1-34)NH₂; [Ser¹, Ile⁵,
 Met⁸, Asn¹⁰, Leu^{11, 28, 31}, His¹⁴, Cha^{22, 23}, Glu^{25, 29},
 Lys^{26, 30}]hPTHrP (1-34)NH₂; [Ser¹, Ile⁵, Cha^{7, 11}, Met⁸,
 Asn¹⁰, His¹⁴, Glu^{22, 25, 29}, Leu^{23, 28, 31}, Lys^{26, 30}]hPTHrP
 (1-34)NH₂; [Ser¹, Ile⁵, Met⁸, Asn¹⁰, His¹⁴, Cha¹⁵, Glu^{22,}
 25 25, 29, Leu^{23, 28, 31}, Lys^{26, 30}]hPTHrP (1-34)NH₂; [Ser¹,
 Ile⁵, Cha^{7, 8}, Asn¹⁰, His¹⁴, Glu^{22, 25, 29}, Leu^{23, 28, 31},
 Lys^{26, 30}]hPTHrP (1-34)NH₂; [Glu^{22, 25, 29}, Leu^{23, 28, 31},
 Lys^{24, 26, 30}]hPTHrP(1-34)NH₂; [Aib²², Leu^{23, 28, 31}, Glu^{25,}
 29, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Glu^{22, 29}, Leu^{23, 28, 31},
 30 Aib²⁵, Lys^{26, 30}]hPTHrP(1-34)NH₂; [Glu^{22, 25, 29}, Leu^{23, 28,}
 31, Aib²⁶, Lys³⁰]hPTHrP (1-34)NH₂; [Glu^{22, 25, 29}, Leu^{23, 28,}
 Lys^{26, 30, 31}] hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Met⁸, Asn¹⁰,
 Leu^{11, 23, 28, 31}, His¹⁴, Cha²², Glu^{25, 29}, Lys^{26, 30}]
 hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Met⁸, Asn¹⁰, Leu^{11, 28, 31},
 35 His¹⁴, Glu^{22, 25, 29}, Lys^{23, 26, 30}]PTHrP(1-34)NH₂; [Ser¹,

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Ile⁵, Met⁸, Asn¹⁰, Leu^{11, 23, 28, 31}, His¹⁴, Glu^{22, 25, 29}, Lys^{26, 27, 30}] hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Met⁸, Asn¹⁰, Leu^{11, 23, 31}, His¹⁴, Glu^{22, 25, 29}, Lys^{26, 28, 30}] hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Met⁸, Asn¹⁰, Leu^{11, 23, 28, 31}, His¹⁴, Glu^{22, 25}, Aib²⁹, Lys^{26, 30}] hPTHrP(1-34)NH₂; [Ser¹, Ile⁵, Met⁸, Asn¹⁰, Leu^{11, 23, 28, 31}, His¹⁴, Glu^{22, 25, 29}, Lys²⁶, Aib³⁰] hPTHrP(1-34)NH₂; or [Ser¹, Ile⁵, Met⁸]hPTHrP(1-34)NH₂.

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala or A₁) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is a side chain of an amino acid (e.g., CH₃ for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of =N-CH(R)-CO-, wherein R is a side chain of an amino acid. β -Nal, Nle, Dap, Cha, Nva, Amp, Pal, and Aib are the abbreviations of the following α -amino acids: β -(2-naphthyl)alanine, norleucine, α,β -diaminopropionic acid, cyclohexylalanine, norvaline, 4-amino-phenylalanine, 3-pyridinylalanine, and α -aminoisobutyric acid, respectively. In the above formula, hydroxyalkyl, hydroxyphenyl-alkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. Also, COE₁ stands for -C=O·E₁. Examples of -C=O·E₁ include, but are not limited to, acetyl and phenylpropionyl.

A peptide of this invention is also denoted herein by another format, e.g., [Cha^{7, 11}]hPTH(1-34)NH₂, with the substituted amino acids from the natural sequence placed between the second set of brackets (e.g., Cha⁷ for Leu⁷, and Cha¹¹ for Leu¹¹ in hPTH). The abbreviation hPTH stands for human PTH, hPTHrP for human PTHrP, rPTH for rat PTH, and bPTH for bovine PTH. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hPTH(1-34) is amino acids 1 through 34 of the peptide sequence for human PTH). The

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sequences for hPTH(1-34), hPTHrP(1-34), bPTH(1-34), and rPTH(1-34) are listed in Nissenson, et al., Receptor, 3:193 (1993). The designation "NH₂" in PTH(1-34)NH₂ indicates that the C-terminus of the peptide is amidated.

5 PTH(1-34), on the other hand, has a free acid C-terminus.

Each of the peptides of the invention is capable of stimulating the growth of bone in a subject (i.e., a mammal such as a human patient). Thus, it is useful in the treatment of osteoporosis and bone fractures when
10 administered alone or concurrently with antiresorptive therapy, e.g., bisphosphonates and calcitonin.

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those
15 formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic
20 acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids).

A therapeutically effective amount of a peptide of this invention and a pharmaceutically acceptable carrier substance (e.g., magnesium carbonate, lactose, or a
25 phospholipid with which the therapeutic compound can form a micelle) together form a therapeutic composition (e.g., a pill, tablet, capsule, or liquid) for administration (e.g., orally, intravenously, transdermally, pulmonarily, vaginally, subcutaneously, nasally, iontophoretically, or
30 by intratracheally) to a subject. The pill, tablet, or capsule that is to be administered orally can be coated with a substance for protecting the active composition from the gastric acid or intestinal enzymes in the stomach for a period of time sufficient to allow it to
35 pass undigested into the small intestine. The

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therapeutic composition can also be in the form of a biodegradable or nonbiodegradable sustained release formulation for subcutaneous or intramuscular administration. See, e.g., U.S. Patents 3,773,919 and
5 4,767,628 and PCT Application No. WO 94/15587. Continuous administration can also be achieved using an implantable or external pump (e.g., INFUSAID™ pump). The administration can also be conducted intermittently, e.g., single daily injection, or continuously at a low
10 dose, e.g., sustained release formulation.

The dose of a peptide of the present invention for treating the above-mentioned diseases or disorders varies depending upon the manner of administration, the age and the body weight of the subject, and the condition of the
15 subject to be treated, and ultimately will be decided by the attending physician or veterinarian.

Also contemplated within the scope of this invention is a peptide covered by the above generic formula for use in treating diseases or disorders
20 associated with deficiency in bone growth or the like, e.g., osteoporosis or fractures.

Other features and advantages of the present invention will be apparent from the detailed description and from the claims.

25 Detailed Description of the Invention

Based on the description herein, the present invention can be utilized to its fullest extent. The following specific examples are to be construed as merely illustrative, and not limitative of the remainder of the
30 disclosure in any way whatsoever. Further, all publications cited herein are incorporated by reference.

Structure

PTH(1-34) has been reported to have two amphophilic alpha helical domains. See, e.g., Barden, et

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al., Biochem., 32:7126 (1992). The first α -helix is formed between amino acid residues 4 through 13, while the second α -helix is formed between amino acid residues 21 through 29. Some peptides of this invention contain
5 the substitution of Cha for one or more residues within or near these two regions of PTH(1-34), e.g., Cha⁷ and Cha¹¹ within the first α -helix or Cha²⁷ and Cha²⁸ within the second α -helix.

Also covered by this invention are variants of
10 PTH(1-34) with the substitution of Aib for a residue adjacent to the α -helixes, e.g., Aib¹⁶, Aib¹⁹, and Aib³⁴; hArg²⁷ and Nle³¹, or the substitution of Dpa for the N-terminal residue.

Synthesis

15 The peptides of the invention can be prepared by standard solid phase synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The following is a description of how [Aib³⁴]hPTH(1-34)NH₂ was prepared. Other peptides of the
20 invention can be prepared in an analogous manner by a person of ordinary skill in the art.

The peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-
25 chemistry solid phase peptide synthesis. See Schnoize, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-Methylbenz-hydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem.,
30 LaJolla, CA) were used with the following side chain protection: Boc-Arg(Tos)-OH, Boc-Asp(OCHx1)-OH, Boc-Asn(Xan)-OH, Boc-Glu(OCHx1)-OH, Boc-His(DNP)-OH, Boc-Asn-GH, Boc-Val-OH, Boc-Leu-OH, Boc-Ser-OH, Boc-Gly-OH, Boc-Met-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-

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Ser(Bzl)-OH, and Boc-Trp(Fm)-OH. The synthesis was carried out on a 0.14 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0
5 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min except for the Boc-Aib-OH and the following residue, Boc-Asn(Xan)-OH, wherein the coupling times were 20 min.

10 At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x
15 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min.), the formyl group on the side chain of Trp was removed by treatment with a solution of 15% ethanolamine/15% water/70% DMF for 2 x 30 min. The partially-deprotected peptide-resin was washed
20 with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc
25 (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on a reversed-phase preparative high pressure liquid chromatography (HPLC) using a reversed phase Vydac™ C₁₈ column (Nest Group, Southborough, MA). The
30 column was eluted with a linear gradient (10% to 45% of solution B over 130 min.) at a flow rate of 10 mL/min (Solution A = 0.1% aqueous TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure
35 product were combined and lyophilized to dryness. 62.3

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mg of a white solid was obtained. Purity was >99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 4054.7 (in agreement with the calculated molecular weight of 5 4054.7).

The synthesis and purification of [Cha^{7,11}]hPTH (1-34)NH₂ was carried out in the same manner as the above synthesis of [Aib³⁴]hPTH(1-34)NH₂. The protected amino acid Boc-Cha-OH was purchased from Bachem, CA. The 10 purity of the final product was >98%, and the electron-spray mass spectrometer gave the molecular weight at 4197.0 (calculated molecular weight is 4196.9).

The full names for the abbreviations used above are as follows: Boc for t-butyloxycarbonyl, HF for 15 hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc 20 for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzoyloxycarbonyl and OcHxl for O-cyclohexyl.

The substituents R₁ and R₂ of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. 25 For example, alkyl groups, e.g., C₁₋₁₂ alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g.,

C₁₋₁₂ hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected 30 with a t-butyl ester. Acyl groups, e.g., COE₁, may be attached by coupling the free acid, e.g., E₁COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride 35 for one hour and cycling the resulting resin through steps (a) to (f) in the above wash program. If the free acid contains a free hydroxy group, e.g., p-

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hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

Other peptides of this invention can be prepared in an analogous manner by a person of ordinary skill in the art.

Functional Assays

A. Binding to PTH Receptor

The peptides of the invention were tested for their ability to bind to the PTH receptor present on SaOS-2 (human osteosarcoma cells). SaOS-2 cells (American Type Culture Collection, Rockville, MD; ATCC #HTB 85) were maintained in RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) and 2 mM glutamine at 37°C in a humidified atmosphere of 5% CO₂ in air. The medium was changed every three or four days, and the cells were subcultured every week by trypsinization.

SaOS-2 cells were maintained for four days until they had reached confluence. The medium was replaced with 5% FBS in RPMI 1640 medium and incubated for 2 hrs at room temperature with 10×10^4 cpm mono-¹²⁵I-[Nle^{8,18}, Tyr³⁴(3-¹²⁵I)] bPTH(1-34)NH₂ in the presence of a competing peptides of the invention at various concentrations between 10⁻¹¹M to 10⁻⁴ M. The cells were washed four times with ice-cold PBS and lysed with 0.1 M NaOH, and the radioactivity associated with the cells was counted in a scintillation counter. Synthesis of mono-¹²⁵I-[Nle^{8,18}, Tyr³⁴(3-¹²⁵I)] bPTH(1-34)NH₂ was carried out as described in Goldman, M.E., et al., Endocrinol., 123:1468 (1988).

The binding assay was conducted with various peptides of the invention, and the IC₅₀ value, (half maximal inhibition of binding of mono-¹²⁵I-[Nle^{8,18}, Tyr³⁴(3-¹²⁵I)]bPTH(1-34)NH₂, for each peptide was calculated.

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As shown in Table I, all of the tested peptides had a high binding affinity for the PTH receptor on the SaOS-2 cell.

B. Stimulation of Adenylate Cyclase Activity

5 The ability of the peptides of the invention to induce a biological response in SaOS-2 cells were measured. More specifically, any stimulation of the adenylate cyclase was determined by measuring the level of synthesis of cAMP (adenosine 3',5'-monophosphate) as
10 described previously in Rodan, et al., J. Clin. Invest. 72: 1511 (1983) and Goldman, et al., Endocrinol., 123:1468 (1988). Confluent SAOS-2 cells in 24 wells plates were incubated with 0.5 μ Ci [3 H]adenine (26.9 Ci/mmol, New England Nuclear, Boston, MA) in fresh medium
15 at 37°C for 2 hrs, and washed twice with Hank's balanced salt solution (Gibco, Gaithersburg, MD). The cells were treated with 1 mM IBMX [isobutylmethyl-xanthine, Sigma, St. Louis, MO] in fresh medium for 15 min, and the peptides of the invention were added to the medium to
20 incubate for 5 min. The reaction was stopped by the addition of 1.2 M trichloroacetic acid (TCA) (Sigma, St. Louis, MO) followed by sample neutralization with 4 N KOH. cAMP was isolated by the two-column chromatographic method (Salmon, et al., 1974, Anal. Biochem. 58, 541).
25 The radioactivity was counted in a scintillation counter (Liquid Scintillation Counter 2200CA, PACKARD, Downers Grove, IL).

The respective EC₅₀ values (half maximal stimulation of adenylate cyclase) for the tested peptides
30 were calculated and shown in Table I. All tested peptides were found to be potent stimulators of adenylate cyclase activity, which is a biochemical pathway indicative as a proximal signal for osteoblast proliferation (e.g., bone growth).

TABLE I

	PEPTIDE	K _d (μM)	EC ₅₀ (nM)
5	[Cha ^{7, 11}]hPTH(1-34)NH ₂	0.01	0.6
	[Cha ²³]hPTH(1-34)NH ₂	0.2	20
	[Cha ²⁴]hPTH(1-34)NH ₂	0.1	10
	[Nle ^{8, 18} , Cha ²⁷]hPTH(1-34)NH ₂ ;	0.05	2
	[Cha ²⁸]hPTH(1-34)NH ₂	0.05	2.5
10	[Cha ³¹]hPTH(1-34)NH ₂	0.03	4
	[Aib ¹⁶]hPTH(1-34)NH ₂ ;	0.004	0.7
	[Aib ¹⁹]hPTH(1-34)NH ₂ ;	0.005	0.6
	[Aib ³⁴]hPTH(1-34)NH ₂ ;	0.007	3
	[Nle ³¹]hPTH(1-34)NH ₂ ;	0.004	0.7
15	[hArg ²⁷]hPTH(1-34)NH ₂	0.007	1
	[Dap, Nle ^{8, 18} , Tyr ³⁴]hPTH(1-34)NH ₂	0.150	10
	[Cha ^{24, 28, 31} , Lys ³⁰]hPTH(1-34)NH ₂ ;	0.5	7
	[Cha ^{7, 11} , Nle ^{8, 18} , Tyr ³⁴]hPTH(1-34)NH ₂	0.006	0.6
	[Cha ^{7, 11} , Nle ^{8, 18} , Aib ^{16, 19} , Tyr ³⁴]hPTH (1-34)NH ₂	0.005	1.5
20	[Cha ^{7, 11} , Nle ^{8, 18, 31} , Aib ^{16, 19} , Tyr ³⁴]hPTH(1-34)NH ₂	0.04	4
	[Cha ¹¹]hPTH(1-34)NH ₂	0.005	2
	[Cha ^{28, 31}]hPTH(1-34)NH ₂	0.06	7
	[Cha ^{7, 11} , Nle ^{8, 18} , Aib ³⁴]hPTH(1-34)NH ₂	0.03	1.5
	[Cha ¹⁵]hPTH(1-34)NH ₂	0.005	1.3
25	[Cha ^{7,11} , Aib ¹⁹]hPTH(1-34)NH ₂	0.007	0.5
	[Cha ^{7,11} , Aib ¹⁶]hPTH(1-34)NH ₂	0.004	1.1
	[Aib ^{16, 19}]hPTH(1-34)NH ₂	0.004	0.6
	[Aib ¹²]hPTH(1-34)NH ₂	0.005	2
	[Aib ³]hPTH(1-34)NH ₂	0.004	1.1
30	[Cha ^{7,11} , Aib ¹⁹ , Lys ³⁰]hPTH(1-34)NH ₂	0.004	2
	[Cha ⁷]hPTH(1-34)NH ₂	0.02	2.3
	[Cha ^{24,28, 31}]hPTH(1-34)NH ₂	1.0	30
	[Aib ¹⁷]hPTH(1-34)	0.05	3
	[Cha ^{7,11,15}]hPTH(1-34)	0.01	1.4

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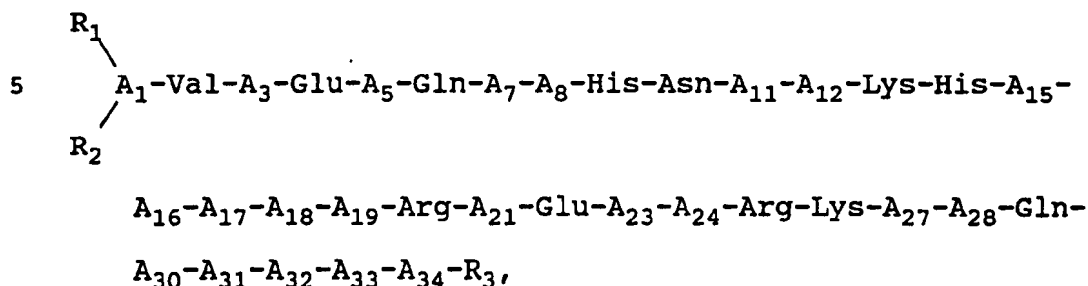
Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is
s intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the claims.

- 20 -

What is claimed is:

1. A peptide of the formula:



10 wherein

- A_1 is Ser, Ala, or Dap;
- A_3 is Ser, Thr, or Aib;
- A_5 is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe or p-X-Phe, in which X is OH, a halogen, or CH_3 ;
- 15 A_7 is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3 ;
- A_8 is Met, Nva, Leu, Val, Ile, Cha, or Nle;
- A_{11} is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe or p-X-Phe in which X is OH, a halogen, or CH_3 ;
- 20 A_{12} is Gly or Aib;
- A_{15} is Leu, Nle, Ile, Cha, β -Nal, Trp, Pal, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3 ;
- A_{16} is Ser, Asn, Ala, or Aib;
- A_{17} is Ser, Thr, or Aib;
- 25 A_{18} is Met, Nva, Leu, Val, Ile, Nle, Cha, or Aib;
- A_{19} is Glu or Aib;
- A_{21} is Val, Cha, or Met;
- A_{23} is Trp or Cha;
- A_{24} is Leu or Cha;
- 30 A_{27} is Lys, Aib, Leu, hArg, Gln, or Cha;
- A_{28} is Leu or Cha;
- A_{30} is Asp or Lys;
- A_{31} is Val, Nle, Cha, or deleted;
- A_{32} is His or deleted;

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- A₃₃ is Asn or deleted;
A₃₄ is Phe, Tyr, Amp, Aib, or deleted;
each of R₁ and R₂ is, independently, H, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀ naphthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀ hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; or one and only one of R₁ and R₂ is COE₁ in which E₁ is C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀ naphthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀ hydroxy-phenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; and R₃ is OH, NH₂, C₁₋₁₂ alkoxy, or NH-Y-CH₂-Z in which Y is a C₁₋₁₂ hydrocarbon moiety and Z is H, OH, CO₂H, or CONH₂;
- provided that at least one of A₅, A₇, A₈, A₁₁, A₁₅, A₁₈, A₂₁, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha, or at least one of A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, and A₃₄ is Aib; or a pharmaceutically acceptable salt thereof.

2. A peptide of claim 1, wherein at least one of A₇, A₁₁, A₁₅, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha; or a pharmaceutically acceptable salt thereof.

3. A peptide of claim 2, wherein
- A₃ is Ser;
A₅ is Ile;
A₇ is Leu or Cha;
A₈ is Met, Nva, Leu, Val, Ile, or Nle;
A₁₁ is Leu or Cha;
A₁₂ is Gly;
A₁₅ is Leu or Cha;
A₁₆ is Asn or Aib;
A₁₇ is Ser;
A₁₈ is Met or Nle;
A₂₁ is Val;
A₂₇ is Lys, hArg, or Cha;

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A₃₂ is His;

A₃₁ is Val, Nle, or Cha;

A₃₃ is Asn;

A₃₄ is Phe, Tyr, Amp, or Aib;

5 R₁ is H;

R₂ is H; and

R₃ is NH₂;

or a pharmaceutically acceptable salt thereof.

4. A peptide of claim 3, wherein at least one of
10 A₇ and A₁₁ is Cha; or a pharmaceutically acceptable salt thereof.

5. A peptide of claim 4, wherein said peptide is
[Cha^{7, 11}]hPTH(1-34)NH₂, [Cha^{7, 11}, Nle^{8, 18}, Tyr³⁴]hPTH(1-
34)NH₂; [Cha¹¹]hPTH(1-34)NH₂; [Cha^{7, 11, 15}]hPTH(1-34)NH₂; or
15 [Cha⁷]hPTH(1-34)NH₂; or a pharmaceutically acceptable salt thereof.

6. A peptide of claim 3, wherein at least one of
A₁₅, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha; or a
pharmaceutically acceptable salt thereof.

20 7. A peptide of claim 6, wherein said peptide is
[Cha²³]hPTH(1-34)NH₂, [Cha²⁴]hPTH(1-34)NH₂, [Nle^{8, 18},
Cha²⁷]hPTH(1-34)NH₂, [Cha²⁸]hPTH(1-34)NH₂, [Cha³¹]hPTH(1-
34)NH₂, [Cha^{24, 28, 31}]hPTH(1-34)NH₂; [Cha^{24, 28, 31},
Lys³⁰]hPTH(1-34)NH₂; [Cha^{28, 31}]hPTH(1-34)NH₂; or
25 [Cha¹⁵]hPTH(1-34)NH₂; or a pharmaceutically acceptable
salt thereof.

8. A peptide of claim 1, wherein at least one of
A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, and A₃₄ is Aib; or a
pharmaceutically acceptable salt thereof.

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9. A peptide of claim 8, wherein
A₃ is Ser or Aib;
A₅ is Ile;
A₇ is Leu or Cha;
5 A₈ is Met, Nva, Leu, Val, Ile, or Nle;
A₁₁ is Leu or Cha;

A₁₅ is Leu or Cha;
A₁₆ is Asn or Aib;
A₁₈ is Met, Aib, or Nle;
10 A₂₁ is Val;
A₂₇ is Lys, Aib, Leu, hArg, or Cha;
A₃₁ is Val, Nle, or Cha;
A₃₂ is His;
A₃₃ is Asn;
15 A₃₄ is Phe, Tyr, Amp, or Aib;
R₁ is H;
R₂ is H; and
R₃ is NH₂;
or a pharmaceutically acceptable salt thereof.
- 20 10. A peptide of claim 9, wherein at least one of
A₃, A₁₂, A₁₆, A₁₇, A₁₉, and A₃₄ is Aib; or a
pharmaceutically acceptable salt thereof.
- 25 11. A peptide of claim 10, wherein said peptide
is [Aib¹⁶]hPTH(1-34)NH₂, [Aib¹⁹]hPTH(1-34)NH₂,
[Aib³⁴]hPTH(1-34)NH₂; [Aib^{16, 19}]hPTH(1-34)NH₂;
[Aib³]hPTH(1-34)NH₂; [Aib¹⁷]hPTH(1-34)NH₂; or
[Aib¹²]hPTH(1-34)NH₂; or a pharmaceutically acceptable
salt thereof.
- 30 12. A peptide of claim 1 wherein at least one of
A₇, A₁₁, A₁₅, A₂₃, A₂₄, A₂₇, A₂₈, and A₃₁ is Cha and at

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least one of A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, and A₃₄ is Aib;
or a pharmaceutically acceptable salt thereof.

13. A peptide of claim 12, wherein
A₃ is Ser or Aib;
5 A₅ is Ile;
A₇ is Leu or Cha;
A₈ is Met, Nva, Leu, Val, Ile, or Nle;
A₁₁ is Leu or Cha;
A₁₅ is Leu or Cha;
10 A₁₆ is Asn or Aib;
A₁₈ is Met, Aib, or Nle;
A₂₁ is Val;
A₂₇ is Lys, Aib, Leu, hArg, or Cha;
A₃₁ is Val, Nle, or Cha;
15 A₃₂ is His;
A₃₃ is Asn;
A₃₄ is Phe, Tye, Amp, or Aib;
R₁ is H;
R₂ is H; and
20 R₃ is NH₂;

or a pharmaceutically acceptable salt thereof.

14. A peptide of claim 13, wherein at least one
of A₇ and A₁₁ is Cha and at least one of A₁₆, A₁₉, and A₃₄
is Aib; or a pharmaceutically acceptable salt thereof.

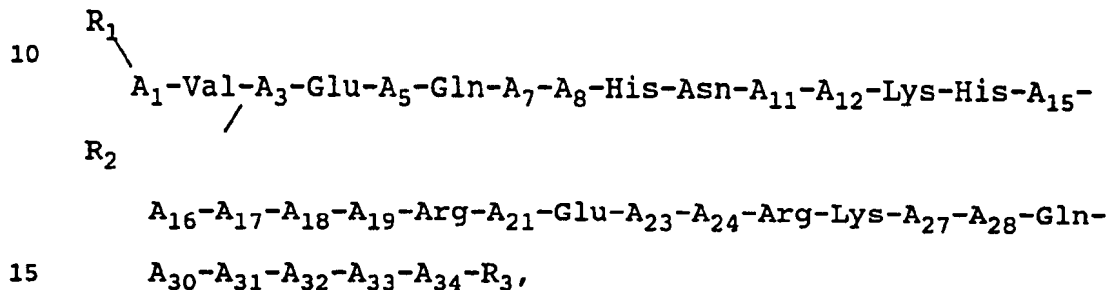
25 15. A peptide of claim 14, wherein said peptide
is [Cha^{7, 11}, Nle^{8, 18}, Aib^{16, 19}, Tyr³⁴]hPTH(1-34)NH₂,
[Cha^{7, 11}, Nle^{8, 18, 31}, Aib^{16, 19}, Tyr³⁴]hPTH(1-34)NH₂;
[Cha^{7, 11}, Aib¹⁹]hPTH(1-34)NH₂; [Cha^{7, 11}, Aib¹⁶]hPTH(1-
34)NH₂; [Cha^{7, 11}, Nle^{8, 18}, Aib³⁴]hPTH(1-34)NH₂; or [Cha^{7,}
30 ¹¹, Aib¹⁹, Lys³⁰]hPTH(1-34)NH₂; or a pharmaceutically
acceptable salt thereof.

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16. A peptide of claim 13, wherein at least one of A₂₄, A₂₈, and A₃₁ is Cha and at least one of A₁₆ and A₁₇ is Aib; or a pharmaceutically acceptable salt thereof.

17. A peptide of claim 16, wherein said peptide
5 is [Cha²⁸, Nle^{8, 18}, Aib^{16, 19}, Tyr³⁴]hPTH(1-34)NH₂, or [Cha²⁸, Aib^{16, 19}] PTH(1-34)NH₂; or a pharmaceutically acceptable salt thereof.

18. A peptide of the formula:



wherein

- A₃ is Ser, Thr, or Aib;
- A₅ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Phe or p-X-Phe, in which X is OH, a halogen, or CH₃;
- 20 A₇ is Leu, Ile, Nle, Cha, β-Nal, Trp, Pal, Phe, or p-X-Phe in which X is H, OH, a halogen, or CH₃;
- A₈ is Met, Nva, Leu, Val, Ile, Cha, or Nle;
- A₁₁ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Phe or p-X-Phe in which X is OH, a halogen, or CH₃;
- 25 A₁₂ is Gly or Aib;
- A₁₅ is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Phe, or p-X-Phe in which X is OH, a halogen, or CH₃;
- A₁₆ is Ser, Asn, Ala, or Aib;
- A₁₇ is Ser, Thr, or Aib;
- 30 A₁₈ is Met, Nva, Leu, Val, Ile, Nle, Cha, or Aib;
- A₁₉ is Glu or Aib;
- A₂₁ is Val, Cha, or Met;
- A₂₃ is Trp or Cha;

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- A₂₄ is Leu or Cha;
A₂₇ is Lys, Aib, Leu, hArg, Gln, or Cha;
A₂₈ is Leu or Cha;
A₃₀ is Asp or Lys;
5 A₃₁ is Val, Nle, Cha, or deleted;
A₃₂ is His or deleted;
A₃₃ is Asn or deleted;
A₃₄ is Phe, Tyr, Amp, Aib, or deleted;
each of R₁ and R₂ is, independently, H, C₁₋₁₂
10 alkyl, C₂₋₁₂ alkenyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀
naphthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀
hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; or
one and only one of R₁ and R₂ is COE₁ in which E₁ is C₁₋₁₂
alkyl, C₂₋₁₂ alkenyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀
15 naphthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀
hydroxy-phenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl;
R₃ is OH, NH₂, C₁₋₁₂ alkoxy, or NH-Y-CH₂-Z in which
Y is a C₁₋₁₂ hydrocarbon moiety and Z is H, OH, CO₂H, or
CONH₂;
20 provided that at least A₁ is Dap, A₇ is β -Nal,
Trp, Pal, Phe, or p-X-Phe; A₁₅ is β -Nal, Trp, Pal, Phe, or
p-X-Phe, A₂₇ is hArg, or A₃₁ is Nle; or a pharmaceutically
acceptable salt thereof.

19. A peptide of claim 18, wherein
25 A₁ is Ser, Gly, or Dap;
A₃ is Ser or Aib;
A₈ is Met, Nva, Leu, Val, Ile, or Nle;
A₁₆ is Asn or Aib;
A₁₈ is Met, Aib, or Nle;
30 A₂₁ is Val;
A₂₇ is Lys, Aib, Leu, hArg, or Cha;
A₃₁ is Val, Nle, or Cha;
A₃₂ is His;
A₃₃ is Asn;

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A₃₄ is Phe, Tyr, Amp, or Aib;

R₁ is H;

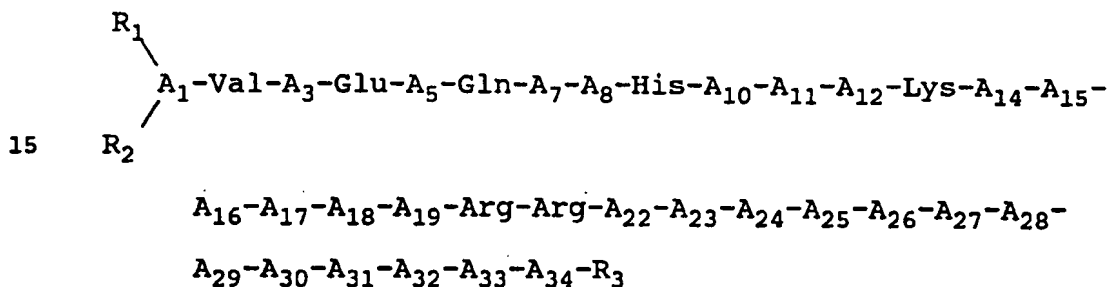
R₂ is H; and

R₃ is NH₂;

5 or a pharmaceutically acceptable salt thereof.

20. A peptide of claim 19, wherein said peptide is [Nle³¹]hPTH(1-34)NH₂, [hArg²⁷]hPTH(1-34)NH₂, or [Dap¹, Nle^{8, 18}, Tyr³⁴]hPTH(1-34)NH₂; or a pharmaceutically acceptable salt thereof.

10 21. A peptide of the formula:



wherein

- 20 A₁ is Ala, Ser, or Dap;
 A₃ is Ser or Aib;
 A₅ is His, Ile, or Cha;
 A₇ is Leu, Cha, Nle, β-Nal, Trp, Pal, Phe, or p-X-Phe in which X is OH, a halogen, or CH₃;
 A₈ is Leu, Met, or Cha;
 25 A₁₀ is Asp or Asn;
 A₁₁ is Lys, Leu, Cha, Phe, or β-Nal;
 A₁₂ is Gly or Aib;
 A₁₄ is Ser or His;
 A₁₅ is Ile, or Cha;
 30 A₁₆ is Gln or Aib;
 A₁₇ is Asp or Aib;
 A₁₈ is Leu, Aib, or Cha;

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- A₁₉ is Arg or Aib;
 A₂₂ is Phe, Glu, Aib, or Cha;
 A₂₃ is Phe, Leu, Lys, or Cha;
 A₂₄ is Leu, Lys, or Cha;
 5 A₂₅ is His, Aib, or Glu;
 A₂₆ is His, Aib, or Lys;
 A₂₇ is Leu, Lys, or Cha;
 A₂₈ is Ile, Leu, Lys, or Cha;
 A₂₉ is Ala, Glu, or Aib;
 10 A₃₀ is Glu, Cha, Aib, or Lys;
 A₃₁ is Ile, Leu, Cha, Lys, or deleted;
 A₃₂ is His or deleted;
 A₃₃ is Thr or deleted;
 A₃₄ is Ala or deleted;
 15 each of R₁ and R₂ is, independently, H, C₁₋₁₂
 alkanyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀ naphthylalkyl, C₁₋₁₂,
 hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀
 hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; or one
 and only one of R₁ and R₂ is COE₁ in which E₁ is C₁₋₁₂
 20 alkyl, C₂₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₇₋₂₀ phenylalkyl, C₁₁₋₂₀
 naphthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀
 hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynaphthylalkyl; and
 R₃ is OH, NH₂, C₁₋₁₂ alkoxy, or NH-Y-CH₂-Z in which
 Y is a C₁₋₁₂ hydrocarbon moiety and Z is H, OH, CO₂H or
 25 CONH₂;
 provided that at least one of A₅, A₇, A₈, A₁₁, A₁₅,
 A₁₈, A₂₂, A₂₃, A₂₄, A₂₇, A₂₈, A₃₀, or A₃₁ is Cha, or at
 least one of A₃, A₁₂, A₁₆, A₁₇, A₁₈, A₁₉, A₂₂, A₂₅, A₂₆,
 A₂₉, A₃₀, or A₃₄ is Aib; or a pharmaceutically acceptable
 30 salt thereof.

22. A peptide of claim 21, wherein at A₂₂ is Phe or Cha; A₂₃ is Phe or Cha; A₂₅ is His; A₂₆ is His; A₂₇ is Leu or Cha; A₂₈ is Ile or Cha; A₂₉ is Ala; A₃₀ is Glu or

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Lys; A₃₁ is Ile or Cha; A₃₂ is His; A₃₃ is Thr; and A₃₄ is Ala; or a pharmaceutically acceptable salt thereof.

23. A peptide of claim 22, wherein at least one of A₇ and A₁₁ is Cha; or a pharmaceutically acceptable salt thereof.

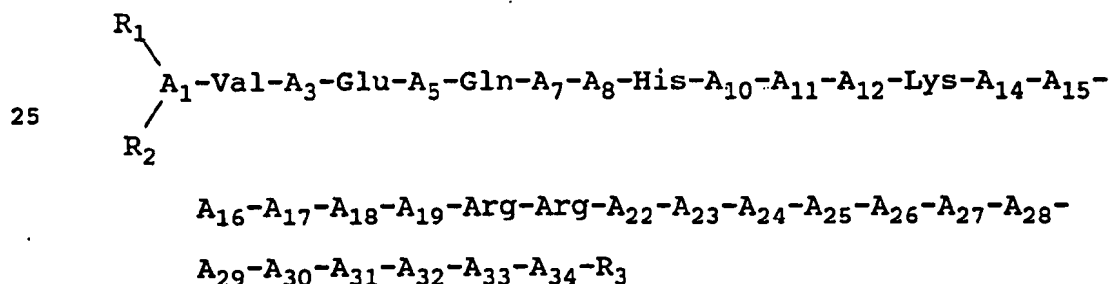
24. A peptide of claim 22, wherein at least one of A₁₆ or A₁₉ is Aib; or a pharmaceutically acceptable salt thereof.

25. A peptide of claim 21, wherein A₂₂ is Glu, Aib, or Cha; A₂₃ is Leu, Lys, or Cha; A₂₅ is Aib or Glu; A₂₆ is Aib or Lys; A₂₈ is Leu, Lys, or Cha; A₂₉ is Glu or Aib; A₃₀ is Cha, Aib, or Lys; A₃₁ is Leu, Cha, or Lys; A₃₂ is His; A₃₃ is Thr; and A₃₄ is Ala; or a pharmaceutically acceptable salt thereof.

26. A peptide of claim 25, wherein at least one of A₇ and A₁₁ is Cha; or a pharmaceutically acceptable salt thereof.

27. A peptide of claim 25, wherein at least one of A₁₆ or A₁₉ is Aib; or a pharmaceutically acceptable salt thereof.

28. A peptide of the formula:



wherein

- 30 -

- A_1 is Ala, Ser, or Dap;
 A_3 is Ser or Aib;
 A_5 is His, Ile, or Cha;
 A_7 is Leu, Cha, Nle, β -Nal, Trp, Pal, Phe, or
5 p-X-Phe in which X is OH, a halogen, or CH_3 ;
 A_8 is Leu, Met, or Cha;
 A_{10} is Asp or Asn;
 A_{11} is Lys, Leu, Cha, Phe, or β -Nal;
 A_{12} is Gly or Aib;
10 A_{14} is Ser or His;
 A_{15} is Ile, or Cha;
 A_{16} is Gln or Aib;
 A_{17} is Asp or Aib;
 A_{18} is Leu, Aib, or Cha;
15 A_{19} is Arg or Aib;
 A_{22} is Phe, Glu, Aib, or Cha;
 A_{23} is Phe, Leu, Lys, or Cha;
 A_{24} is Leu, Lys, or Cha;
 A_{25} is His, Aib, or Glu;
20 A_{26} is His, Aib, or Lys;
 A_{27} is Leu, Lys, or Cha;
 A_{28} is Ile, Leu, Lys, or Cha;
 A_{29} is Ala, Glu, or Aib;
 A_{30} is Glu, Cha, Aib, or Lys;
25 A_{31} is Ile, Leu, Cha, Lys, or deleted;
 A_{32} is His or deleted;
 A_{33} is Thr or deleted;
 A_{34} is Ala or deleted;
each of R_1 and R_2 is, independently, H, C_{1-12}
30 alkanyl, C_{7-20} phenylalkyl, C_{11-20} naphthylalkyl, C_{1-12} ,
hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20}
hydroxyphenylalkyl, or C_{11-20} hydroxynaphthylalkyl; or one
and only one of R_1 and R_2 is COE_1 in which E_1 is C_{1-12}
alkyl, C_{2-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20}

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napthylalkyl, C₁₋₁₂ hydroxyalkyl, C₂₋₁₂ hydroxyalkenyl, C₇₋₂₀ hydroxyphenylalkyl, or C₁₁₋₂₀ hydroxynapthylalkyl; and

R₃ is OH, NH₂, C₁₋₁₂ alkoxy, or NH-Y-CH₂-Z in which Y is a C₁₋₁₂ hydrocarbon moiety and Z is H, OH, CO₂H or
5 CONH₂;

provided that at least one of A₂₃, A₂₄, A₂₇, A₂₈, or A₃₁ is Lys; or a pharmaceutically acceptable salt thereof.

29. A peptide of claim 28, wherein A₂₂ is Glu,
10 Aib, or Cha; A₂₃ is Leu, Lys, or Cha; A₂₅ is Aib or Glu; A₂₆ is Aib or Lys; A₂₈ is Leu, Lys, or Cha; A₂₉ is Glu or Aib; A₃₀ is Cha, Aib, or Lys; A₃₁ is Leu, Cha, or Lys; A₃₂ is His; A₃₃ is Thr; and A₃₄ is Ala; or a pharmaceutically acceptable salt thereof.

15 30. A peptide of claim 29, wherein at least one of A₇ and A₁₁ is Cha; or a pharmaceutically acceptable salt thereof.

31. A peptide of claim 29, wherein at least one of A₁₆ or A₁₉ is Aib; or a pharmaceutically acceptable salt
20 thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/11292**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 38/29; C07K 1/06, 14/635

US CL : 436/86; 530/324, 399; 514/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/86; 530/324, 399; 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG

search terms: parathyroid hormone, parathyroid hormone related protein, PTH, PTHrP, derivatives, analogs, analogues

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOREV et al. Modifications of Position 12 in Parathyroid Hormone and Parathyroid Hormone Related Protein: Toward the Design of Highly Potent Antagonists. Biochemistry. 1990, Vol. 29, No. 6, pages 1580-1586.	1, 8-11, 21, 28
Y	WO 94/02510 A2 (SANDOZ-ERFINDUNGEN VERWALTUNGSGELLSCHAFT) 03 February 1994, page 1, Abstract, page 74, lines 22 - 27.	1 and 8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 SEPTEMBER 1996

Date of mailing of the international search report

16 OCT 1996

Name and mailing address of the ISA/US
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